Microchip-Induced Tumors in Laboratory Rodents and Dogs: A Review of the Literature 1990–2006

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Abstract

This paper reviews literature published in oncology and toxicology journals between 1990 and 2006 addressing the effects of implanted radio-frequency (RFID) microchips on laboratory rodents and dogs. Eleven articles were reviewed in all, with eight investigating mice and rats, and three investigating dogs. In all but three of the articles, researchers observed that malignant sarcomas and other cancers formed around or adjacent to the implanted microchips. The tumors developed in both experimental and control animals, and in two household pets. In nearly all cases, researchers concluded that the microchips had induced the cancers. Possible explanations for the tumors are explored, and a set of recommendations for policy makers, human patients and their doctors, veterinarians, pet owners, and oncology researchers is presented in light of these findings.

1. Introduction

Since their introduction in the late 1980's, injectable, glass-encapsulated radio-frequency (RFID) transponders, known colloquially as microchip implants, have become the industry standard for identifying mice and rats used in laboratory research. Animal shelters and veterinarians now routinely inject the devices into dogs and cats. More recently, there has been a push to implant microchips into people to secure building access, to manage medical records, and to identify elderly patients.

American workers at the now-defunct CityWatcher surveillance company [1] and officials with the Mexican Attorney General's office [2] were microchipped for workplace security reasons. Concern that the practice of microchipping employees could spread has raised the specter of Big Brother and prompted lawmakers in several states to pass laws preventing the forced or coerced implantation of microchips in human beings.

Microchip implantation is controversial for many reasons, but question of whether or not it is safe to implant a microchip into human flesh has only recently been raised. When the FDA approved the VeriChip implant for human use in October 2004, the public saw the approval as evidence that the device had been thoroughly tested and found to be safe.

However, a series of studies dating back to 1996 shows a link between the microchips and cancer in laboratory mice and rats. These articles received very little attention outside of toxicology laboratories until September 2007, when The Associated Press published an article that brought the studies to the attention of the American public and the world at large [3].

There is now an ongoing debate regarding the safety of the chips. As a result of lobby pressure combined with heavy advertising by Schering Plough for its HomeAgain pet recovery system, close to 5% of the United States' estimated 164 million dogs and cats have now been chipped [4]. Animal shelters around the United States now routinely chip dogs and cats before releasing them for adoption, and governments, including those of Portugal, Singapore, Bangkok, Los Angeles County, and El Paso, Texas, have passed ordinances requiring that all dogs under their jurisdiction be microchipped. El Paso has extended the chipping mandate to cats and ferrets, as well.

Horses are also being chipped, and the USDA has approved equine implants as part of a proposed national animal identification system for farm animals.

On the human side, an estimated 300 Americans and 2,000 people worldwide have been implanted with microchip transponders. In early 2007, the VeriChip Corporation (now known as the Positive ID Corporation) implanted Alzheimer's patients and their caregivers with microchips as part of a research study. The study raised ethical questions about the use of Alzheimer's patients, since they have reduced mental capacity and could not give informed consent.

It appears that none of the people implanted with microchips were told of potential health risks prior to the publication of the Associated Press article in 2007.

This literature review was undertaken to consolidate nearly two decades of research on animals into the safety of implantable microchips. Proposed explanations for the cancer findings are discussed, and other adverse reactions from the implant are reviewed. The paper concludes with a discussion of how the findings may impact implanted human beings and pets, and concludes with a list of recommendations.

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2. Methodology

The articles included in this review were found in 2007 through a search of the PubMed online medical research database (online at www.PubMed.gov), using search terms related to implantable microchips, safety, dogs, animals, cancer, and adverse reactions. All articles found that addressed the safety of implantable microchips were reviewed. When those articles referenced other articles, they were in turn obtained and reviewed as well. Eleven articles in total were found in this way and are discussed in the following sections.

3. Summary of the Literature

3.1. Cancer Found in Mice and Rats

In six studies published in toxicology and pathology journals between 1996 and 2006, researchers found a causal link between implanted microchip transponders and cancer in laboratory mice and rats [5-10]. The tumors were typically sarcomas, including fibrosarcomas. Other cancers found included rhabdomyosarcoma, leiomyosarcoma, malignant fibrous histiocytoma, mammary gland adenocarcinoma, malignant schwannoma, anaplastic sarcoma, and histiocytic sarcoma.

In almost all cases, the tumors arose at the site of the implants and grew to surround and fully encase the devices. In several cases the tumors also metastasized or spread to other parts of the animals, including the lungs, liver, stomach, pancreas, thymus, heart, spleen, lymph nodes, and musculature of the foreleg.

The tumors generally occurred in the second year of the studies, after half a lifetime of implant exposure when the animals were in middle to advancing age. Only in the Blanchard study did genetically modified mice develop fast- growing cancers before six months [7].

The percentage of mice and rats developing microchip-induced tumors ranged from 0.8% to 10.2%. These findings are summarized in Table 1.

Several researchers, including Elcock et al. [6], Le Calvez et al. [5], and Tillmann et al. [9], suggest that the actual rate of tumor formation may have been higher than reported in their studies, since they examined only visible lesions rather than microscopic changes that could signal the onset of additional tumors.

3.2. Cancer Found in Dogs

Two studies evaluated cancerous tumors (fibrosarcoma and liposarcoma) in companion dogs. One tumor was adjacent to the microchip [11] and the other completely surrounded the microchip [12].

3.3. Studies in which Cancer was not Found

Three of the eleven studies examined implanted dogs [13], rats [14], and mice [15] without finding evidence of cancerous tumors. These studies have been cited as evidence that implantable microchips are safe. However, a closer examination of the studies reveals methodological limitations that call their statistical validity into question. Problems with the studies include the extremely small number of animals used and short microchip exposure time. Findings from these studies are summarized in Table 2.

3.4. Animals Used in the Research

Toxicology and carcinogenicity researchers rely on laboratory animals to determine whether substances are safe or potentially harmful. Since most substances that cause cancer in humans also cause cancer in mice and rats, these animals can serve as an early indicator that a substance may not be safe for use in humans.

Several strains of laboratory mice and rats were evaluated in the rodent studies, including B63F1 mice, CBA/J mice, p53+/- transgenic mice, Fischer 344 rats, and Sprague-Dawley rats. The dogs involved in studies included one beagle, one French bulldog, and several mixed-breed dogs. A listing of the animals involved in each research study appears in Table 3.

Rodents used in laboratory studies are specially bred for uniformity and hardiness. They are used in cancer studies for their ability to respond to carcinogenic substances yet remain relatively free from spontaneous tumors that are unrelated to carcinogenic test substances.

The B6C3F1 mouse was used in four of the eight rodent studies. The Handbook of Carcinogen Testing states that this mouse is used for cancer research because it is "hardy, easy to breed, disease resistant, and has a low spontaneous tumor incidence at most sites" [16].

The p53+/- mouse contains a genetic mutation in the p53 gene which normally sends protein to help repair damaged cells. In these mice, one allele, or portion of the gene has been deleted, thus increasing their susceptibility to cancer caused by genotoxins, or substances that damage genetic material. These mice are not known to develop spontaneous cancers in the first six months of life and are expected to only develop cancer in the presence of genotoxins. The high rate of cancer in p53+/- mice at less than six months suggests that the implant may have genotoxic attributes.

The CBA/J mouse is an inbred strain widely used as a general purpose laboratory animal. It suffers from

hereditary blindness, making it of interest to vision researchers, and rarely develops mammary tumors [17]. The CD-1 (albino) mouse is described as a "general multipurpose model [for] safety and efficacy testing, aging, surgical model, [and] pseudopregnancy" [18].

The Sprague-Dawley rat is described as "a general model for the study of human health and disease" and an "excellent model for toxicology, reproduction, pharmacology, and behavioral research areas." It has a life span of 2.5 – 3.5 years [19]. The Fischer 344 rat is described as the "most widely used inbred rat strain, particularly for toxicology and teratology" studies [20].

3.5. Implantable Microchips Used

The microchip transponders used in the animal studies were provided by BioMedic Data Systems Inc, LifeChip by Destron Fearing, and Merial Indexel® by Digital Angel Additional information appears in Table 4.

Table 1. Studies that found microchip-induced cancer (in reverse chronological order)

Author(s)	Species	# of animals	Length of Implant Exposure	Developed Cancer
Le Calvez et al., 2006	mice	1,260	2 years	4.1%
Vascellari et al., 2006	dog	N/A	7 months (at age 9)	1 dog
Vascellari et al., 2004	dog	N/A	18 months (at age 11)	1 dog
Elcock et al., 2001	rats	1,040	2 years	0.8%
Blanchard et al., 1999	mice	177	6 months	10.2%
Palmer et al., 1998	mice	800	2 years	2.0%
Tillmann et al., 1997	mice	4,279	lifespan	0.8%
Johnson, 1996	mice	2,000	2 years	~1.0%

This table examines studies where cancer developed after microchip exposure. It denotes the animal species, sample size, duration of exposure, and rate of cancer for each group of animals.

Table 2. Studies that did not find microchip-induced cancer (in reverse chronological order)

Author(s)	Species	# of animals	Length of Implant Exposure	Developed Cancer
Murasugi et al., 2003	dogs	2	3 days	none observed
		2	3 months	
		2	1 year	
		2	3 years	
		1	6 years	
Ball et al., 1991	rats	10	2 weeks	none observed
		10	3 months	
		10	6 months	
		10	1 year	
Rao & Edmondson, 1990	mice	10	3 months	none observed
		10	15 months	
		74	2 years	
		39	< 2 years	

This table presents studies in which cancer was not found after microchip exposure. It denotes the species, sample size, and duration of exposure to the implant.

Table 3: Animals examined in the studies, identified by breed or strain

Author(s)	# of Animals	Type of Animal Studied	Developed Cancer
Le Calvez et al., 2006	1,260	B6C3F1 mice	4.1%
Elcock et al., 2001	1,040	Fischer 344 rats	0.8%
Blanchard et al., 1999	177	*p53+/-* transgenic mice	10.2%
Palmer et al., 1998	800	B6C3F1/CrlBR VAF/Plus mice	2.0%
Tillmann et al., 1997	4,279	CBA/J mice	0.8%
Johnson, 1996	2,000	B6C3F1 mice and CD1 ("albino") mice	~1.0%
Murasugi et al., 2003	9	Beagle; mixed breed dogs	none observed
Ball et al., 1991	40	Sprague-Dawley rats	none observed
Rao & Edmondson, 1990	140	B6C3F1 mice	none observed
Vascellari, 2006	1	French bulldog	1 dog
Vascellari, 2004	1	Mixed breed dog	1 dog

This table indicates the breed or strain of animal evaluated in each study. Animals in the first group of studies developed microchip-induced tumors. Animals in the second group did not develop tumors. The third group are the dogs that developed cancer around or attached to microchip implants.

Table 4. Microchip implants used in the studies, identified by brand name or supplier

Author(s)	Microchip used	Developed Cancer
Le Calvez et al., 2006	BioMedic Data Systems Inc.	4.1%
Elcock et al., 2001	BioMedic Data Systems Inc.	1.0%
Blanchard et al., 1999	BioMedic Data Systems Inc.	10.2%
Palmer et al., 1998	Unspecified	2.0%
Tillmann et al., 1997	BioMedic Data Systems Inc.	0.8%
Johnson, 1996	BioMedic Data Systems Inc.	~1.0%
Murasugi et al., 2003	LifeChip; Destron Fearing.	none observed
Ball et al., 1991	BioMedic Data Systems Inc.	none observed
Rao & Edmondson, 1990	BioMedic Data Systems Inc.	none observed
Vascellari, 2006	Merial Indexel® (Digital Angel)	1 dog
Vascellari, 2004	Merial Indexel® (Digital Angel)	1 dog

This table indicates the manufacturer and brand of microchips used in each study. Animals in the first group of studies developed microchip-induced tumors, whereas animals in the second group did not develop tumors. The third group are the dogs that developed cancer around or attached to the microchip implants.

4. Explanation for the Tumors

4.1. Cancer Was Caused by the Implants

In six of the studies, researchers clearly identified a causal link between the cancers found and the implanted microchip transponder. Tillmann et al. [9] state "The neoplasms induced in the present investigation are clearly due to the implanted microchips" [p. 200]. Elcock et al. [6] refer to the tumors as "microchip-induced" [p. 491]. Le Calvez et al. [5] directly attribute the tumors to the microchips. And Blanchard et al. [7] state: "there was an unequivocal association between the [microchip implant] transponder and sarcoma that was unrelated to drug treatment" [p. 526].

The mention to drug treatment refers to the fact that several studies initially began as toxicology research designed to evaluate the safety of chemical compounds unrelated to the microchip. The animals were microchipped for identification purposes. However, when both experimental and control animals began to develop cancerous tumors around the microchips, the researchers shifted their attention to the implants themselves.

Johnson [10] observed that animals that were microchipped and then treated with a chemical test substance, as well as control animals that had received the microchip only, both developed tumors around the device at approximately the same rate, thus ruling out the chemical substance as the cause of the tumor. Palmer et al. [8] also observed that tumors occurred in control animals as well as experimental animals, and that "all tumors were observed…at or near the implantation site…[and] were attached to the implant or partially or totally encased the implant" [p. 170].

4.2. Hypotheses

At the present time, there is no definitive, universally accepted explanation as to why implanted microchips have caused malignant tumors in mice, rats, and dogs. The following are among some of the explanations that have been proposed:

(1) **Foreign-Body Tumorigenesis**: The presence of the microchip, a subcutaneous foreign body, may cause cellular changes that can lead to cancer.

(2) **Post-Injection Sarcoma**: Inflammation from the chip-injection procedure may cause cellular changes that can lead to cancer.

(3) **Possible Genotoxic Properties of the Implant**: The glass capsule or polypropylene sheath surrounding it may have carcinogenic or genotoxic properties, or its presence within the host may give rise to genotoxic byproducts.

(4) **Radio-Frequency Energy Emissions from the Transponder or Read**er: The radio- frequency energy involved with the transponder may somehow contribute to tumor formation.

Each hypothesis is addressed below.

4.3. Foreign-Body Tumorigenesis

It is known that implanted foreign bodies can cause cancer both in animals and humans. McCarthy et al. [21] reported on a liposarcoma in a dog where a glass foreign body had lodged 10 years previously. Brand and colleagues [22] observed that rodents are particularly susceptible to developing tumors in response to foreign bodies, and produced a substantial amount of research on the topic. Compelling evidence indicates that foreign-body tumorigenesis is also operative in humans, as discussed later in this paper.

Foreign-body-induced tumors can pose serious threats to animal health. Elcock et al. [6] report from their review of prior literature that most tumors arising from foreign bodies are malignant mesenchymal neoplasms with a rapid growth rate, killing the animal in a matter of weeks.

Brand's research revealed that the size and surface of the foreign body are the key characteristics affecting tumor development. Although it may seem counter-intuitive, research shows that foreign bodies with smooth, continuous surfaces are actually more carcinogenic than those with rough, scratched, or porous surfaces.

The surface of the foreign body determines, in part, the length of the period of active inflammation. Rough, irregular surfaces have a longer active inflammatory phase before the foreign body is encapsulated in fibrous tissue. An extended period of inflammation is associated with lower rates of tumor development. In contrast, smooth surfaces have a shorter inflammatory period and thus are more likely to lead to tumors [6].

The microchip implant has both a smooth, homogeneous surface in the glass capsule and a rougher portion coated in a polypropylene substance that is designed to prevent migration. Ball's team [14] described the surface of the implant as follows: "The glass capsule had a smooth, homogeneous surface. The polypropylene sheath that covered one end of the transponder had a manufactured hole at its closed end. Its surface was characterized by scratches, ridges, and other irregularities" [14]

In relation to the microchip implant, Elcock et al. [6] write: "A chronic foreign body such as the electronic microchip, surrounded by a rim of mature fibrous connective tissue with little or no active inflammation may

. . . be more tumorigenic than one with ongoing active inflammation" [6] p. 490].

On the basis of these prior observations from the literature, it might be predicted that the cancer would form around the smooth portion of the implant first. However, Blanchard et al. [7] reported that tumors in their study arose at the microchip's "plastic anchoring barb" and then expanded to eventually surround the rest of the device. They write: "It appeared that tumor(s) arose in the mesenchymal tissue surrounding the polypropylene component of the transponder, initially involving the barbed area and then in some cases extending completely around the entire transponder site" [p. 523].

Further study is needed to better understand this issue.

4.4. Post-Injection Sarcoma

"[I]rritation, inflammation, and/or wounds. . . [promote] tumor development. Virtually anything that causes a local inflammatory reaction may potentially be responsible for neoplastic [cancer] initiation."

–Vascellari et al., 2006 [11]

The implantation of a microchip requires the insertion of a relatively large 12-gauge needle into an animal's flesh. That procedure alone may be problematic, as research indicates that inflammation resulting from injections can predispose tissues to developing cancer. The resulting malignancies are known in the veterinary literature as post-injection sarcomas.

Vascellari et al. [11] suggest that the tumor they evaluated in a French bulldog may have been this type of post-injection sarcoma, caused either by the injection of the microchip or by injection of vaccines that the dog received at the same site.

In light of the potential for post-injection sarcomas to develop in dogs, it would seem prudent to reduce inflammatory injection reactions in dogs (and cats) as much as possible. Given these findings, veterinarians should identify the location of microchip implants in chipped animals and avoid using the same site for vaccinations or other injections.

4.5. Possible Genotoxic Properties of the Implant

In the Blanchard [7] study over 10% of p53+/- mice developed malignancies around the implants. This finding was especially noteworthy, since the mice used in the study were genetically modified to develop tumors specifically in response to exposure to mutagens and genotoxins (toxic substances that affect genetic material). The genetic modification undergone by these mice "appears to be without effect on the development of spontaneous tumors...but it imparts exquisite sensitivity to the mutational and carcinogenic effects of genotoxic chemicals" [p. 524].

The researchers observe that "the glass and polypropylene components of the [implanted microchip]…are generally assumed to be devoid of mutagenic and/or cytotoxic components" [p. 519]. However, the fact that these mice developed cancer at such a high rate on exposure to the microchip was puzzling. The discrepancy suggested that something other than a foreign-body reaction or an injection response may be involved in the microchip-induced cancers found in these mice. The researchers suggest that "the presence of the foreign body may elicit tissue reactions capable of generating genotoxic byproducts" [p. 526] and provide technical descriptions of several processes through which this may occur.

It is unclear whether the suspected genotoxic byproducts were produced by the implant directly or through processes occurring in the surrounding tissues of the host animals – or a combination of the two. As mentioned previously, the mice used in the Blanchard study are genetically modified to lack a portion of the p53 gene that normally aids in the repair of damaged cells. The higher rate of malignancy seen in these animals may result from their inability to repair cellular damage resulting from the implant.

The Blanchard report does not evaluate the biocompatibility of the polypropylene polymer sheath, but does note that the observed tumors arose in the tissue surrounding the polypropylene component of the transponder. (As noted above, the tumors began at the microchip's plastic anchoring barb and expanded to eventually surround the rest of the device.) This suggests another possibility: that "leachates," or substances leaching from the implant into the surrounding tissue, may be involved in the tumorigenesis [p. 525].

A literature review into the safety of the polymer sheath was beyond the scope of this paper. Such a review would contribute to a more complete discussion of this process.

4.6. Radio-Frequency Energy Emissions from the Transponder or the Reader

Blanchard et al. [7] also raise the possibility that "energy from the signal transmitted by the transponder [may be] carcinogenic" [p. 525]. Though there is a tendency to think of microchip implants as biologically inert because of the materials in which they are encapsulated, it should be remembered that implantable microchips are actually radio-frequency transponders designed to pick up and amplify ambient electromagnetic frequency (EMF) radiation. The long-term effects of having a reactive, foreign-body capsule in the body that

absorbs and responds to electromagnetic energy are unknown.

Based on a review of published accounts, the role that EMF radiation may play in the development of microchip-induced tumors appears not to have been well studied. Blanchard et al. believe that "these variables warrant further examination" [p. 525].

5. Differences between Species

An important factor to consider when interpreting animal studies is whether findings in one breed or species are applicable to other animals or to humans. This section examines that issue.

5.1. Possible Difference in Tumor Susceptibility Between Different Strains of Mice

In the studies where microchip-induced malignant tumors were found, the percentage of mice affected ranged from a low of 0.8% in the CBA/J mouse [9] to a high of 10.2% in the p53+/- mouse [7]. This wide variation suggests that different strains of mice may have different degrees of susceptibility to cancer from the implants.

Le Calvez et al. [5], Palmer et al. [8], and Elcock et al. [6] all suggest a strain difference, with Palmer and Elcock observing that no implant-induced sarcomas have been reported in the CD-1 mouse strain, for example. However, Johnson [10], whose study of both B6C3F1 mice and CD1 mice found a ~1% overall incidence of microchip-induced tumors, believes that CD1 mice in his study "probably did" develop foreign-body sarcomas around the implanted microchips [23]. Nonetheless, it appears that different strains of mice may develop microchip-induced cancers at differing rates.

5.2. Tumor Susceptibility across Species

It has long been observed that different species have differing levels of susceptibility to foreign-body tumors. As reported in Rao and Edmondson [15], evaluation of prior research shows that mice, rats, and to some extent, dogs are more susceptible to foreign body tumorigenesis than guinea pigs, chickens, and hamsters, for instance [24].

The fact that rodents and dogs have developed cancer in response to implants does not necessarily mean that humans will do the same. Blanchard et al. [7] caution that "blind leaps from the detection of tumors to the prediction of human health risk should be avoided" [p. 526]. In humans, Elcock et al. [6] point out that fibrotic scar formation proceeds at a much slower rate than in rodents, which might indicate that humans are more resistant to foreign-body-induced tumors than rats and mice [p. 491].

5.3. Humans are Susceptible to Foreign-Body Carcinogenesis

Nevertheless, according to Elcock's summary of the literature on foreign-body tumorigenesis, any inert substance inserted into the body for long periods can produce neoplasia (abnormal tissue growth), including in humans [p. 489]. Vascellari et al. [12] note that foreign-body-induced sarcomas, including osteosarcomas, rhabdomyosarcomas. haemangiosarcomas, and liposarcomas, have been described in humans, although with a low prevalence [p. 190].

Most of the malignant, microchip-induced tumors in rodents reviewed in the present report were classified as sarcomas – soft tissue cancers that afflict the muscles, tendons, fibrous tissues, fat, blood vessels, and nerves. The following is a brief description of this type of cancer in human beings from Blake Morrison [25] of Baylor University Medical Center:

"*Soft tissue sarcomas are a diverse group of neoplasms that arise in the connective tissues throughout the body. They account for approximately 1% of adult malignancies and 7% to 15% of pediatric malignancies. About 50% to 60% of sarcomas occur in the extremities* [the arms and legs]*, and although they are rare, they are responsible for more deaths than testicular cancer, Hodgkin's disease, and thyroid cancer combined. These tumors are notorious for recurring and metastasizing—often with devastating results—despite apparently complete resection....The National Cancer Institute's Cancer Surveillance, Epidemiology, and End-Result (SEER) Program in 1996 reported 6400 new cases of soft tissue sarcoma, including 3500 in males and 2900 in females, for a male-to-female ratio of about 1.2:1.*"

Sarcomas can arise in human beings in scar tissue as a result of "foreign body implantation" among other causes, according to Kasper et al. [26].

Jennings et al. [27] reviewed published research involving six cases of angiosarcoma and 40 cases of sarcomas of other types associated with foreign-body material in humans. They found that these cases "provide compelling evidence that solid-state [foreign-body] tumorigenesis is operative in humans" [p. 2443], and note that "implanted foreign material...should be considered capable of inducing virtually any form of sarcoma in humans" [p. 2436].

Jennings et al. describe each of the three cases investigated in their study as "a high-grade tumor, which metastasized and led to the death of the patient" [p. 2443]. In commenting on cases from the prior literature, they observe that the malignancies developed between four

months and 63 years after exposure to the foreign body, and that the foreign-body related sarcomas "appear to be highly aggressive, both morphologically and biologically" [p. 2443].

Other researchers have also found highly aggressive sarcomas and carcinomas developing in humans around or near implants, including pacemakers [28-30], vagus nerve stimulators [31], and orthopedic implants [32]. Based on these findings, researchers recommend that all material found near implants that is removed from patients should be carefully examined for cancerous changes.

In another case, surgical threads found within and near a malignant tumor were believed to have induced tumorigenesis [33]. The researchers reporting that case cite Brand's animal studies which indicate that the physical presence of the foreign bodies, rather than their chemical components, may be responsible for tumorigenesis, and point out that the most critical factor in the induction of these sarcomas is the formation of a fibrous capsule around the foreign body. They note that "in our case the persistence of a foreign body...and the presence of large extensive fibrosis areas in the tumor seem to be in agreement with this possibility" [33].

Brand et al. [22], reporting on rodent studies, note that removing the foreign body may not be enough to prevent the development of cancer once the tumorigenesis process is underway. They write: "As reported in the literature and infrequently observed in our laboratory, removal of the [foreign body] implant from the tissue capsule during the late preneoplastic period does not always abort development of tumors from the remaining empty capsule....However, removal of the [foreign body] left a solid collagenous, possibly even calcifying or ossifying, scar that failed to resolve and therefore acted like [foreign body] material. The latter explanation may underline the occurrence of scar-related sarcomas in man, as reported in the literature" [p. 283].

6. Other Adverse Reactions to the Implants

Several of the studies reviewed for this report discussed other problems related to the implantable microchips, including migration (shifting location in the body), incorrect insertion, failure to work, and loss from the body.

6.1. Migration

Despite the presence of the polypropylene sheath designed to anchor the implanted microchip, chip migration appears to be an ongoing problem. Le Calvez et al. [5] found that microchips that had migrated from the initial implantation site accounted for 19.3% of the tumors they observed. Although the devices were originally injected into the backs of the animals, the microchip-associated tumors were later found in the limbs (4/52), the abdominal region (4/52), and the dorsal head (1/52) [p. 259].

Murasugi et al. [13] reported no cases of migration in their study of nine dogs. However, Jansen et al. [34] found that about half of the transponders inserted into the shoulders of beagle dogs in a four-month study had migrated to some extent. Reports from veterinarians also indicate that migration is a problem in dogs. In the United Kingdom, a voluntary registry of adverse reactions to microchip implants has been maintained by the British Small Animal Veterinary Association (BSAVA) for several years. Migration is the most common problem reported to the BSAVA, with "the elbow and shoulder being the favourite locations of wayward microchips" [35]. The BSAVA reports that "it is surprising how quickly some microchips migrate," noting that microchips have been found in a different location as little as one week after implantation or up to ten years later [36]. Over 180 cases of migration were reported to the BSAVA between 1996 and 2006.

6.2. Injection Error

Occasionally, due to technician error, implants are injected into the wrong site on animals. Rao and Edmondson [15] reported that 5% (7 of 140) of the microchips used in their study were later found in the perirenal area (in the abdominal cavity, surrounding the kidneys) instead of in the correct implant area just under the skin on the back. They surmise that the implants either migrated or had been injected incorrectly directly into the abdomen. Johnson [37] reported similar problems, stating, "occasionally some would be inserted too deep, the needle that put them in was probably held at the wrong angle."

Like migration, the danger of incorrect injection also poses a risk to pets. The BSAVA cautions that technicians must be properly trained to perform the implant procedure, citing a "disastrous" incident in 2004 where an attempt to implant a struggling kitten resulted in its sudden death. A post-mortem examination later revealed that the microchip had been accidentally inserted into the kitten's brainstem [35]. In another case a cat suffered severe neurological damage when a microchip was accidentally injected into its spinal column [38].

6.3. Failure and Loss of Transponder

Other problems with the microchips include failure to function, in which the microchip ceases to respond to a query from the reader device, and loss, where the microchip exits the body. Rao and Edmondson [15] reported that four of the 140 implants used in their study

failed due to microscopic cracks in the weld connecting the antenna leads to the microchip or leakage of the glass capsule resulting in fluid accumulation around the microchip [p. 413].

Rao and Edmondson also reported that an additional two of the 140 microchips in their study were lost, including one microchip lodged in the subcutaneous tissue over the lumbar vertebrae that was pushed out slowly through the scar tissue of the injection site during the tenth month after implantation.

In the Tillmann [9] study, 1.5% of 4,279 (approximately 64) implanted microchips had to be substituted with new transponders when they either ceased functioning or were lost from the body and later found in the softwood of the animals' cages. Most of the losses occurred in the first two days after implantation, but some occurred as long as seven months later.

Johnson [37] also reported that failure and loss was an issue, stating: "We had a few [chips] early in the studies that would migrate out if the wound wasn't healing properly."

6.4. Adverse Reactions Likely Under-Reported

It is likely that the true rate of microchip adverse reactions in the studies was higher than reported, since the purpose of the articles was to discuss microchip-induced cancer, not other complications. One indication that this may be the case is Johnson's [37] personal communication reporting failure, loss, and migration, as discussed above. Though these events did occur, they were not reported in his original published paper and were only solicited in response to a specific inquiry. It is possible that other investigators may have likewise neglected to mention such reactions when they occurred.

Adverse reactions to microchips implanted in dogs and cats may also be substantially underreported. The BSAVA, in its 2003 microchip report, stated that "2003 saw a marked increase in the number of reports received through the Adverse Reaction Reporting Scheme. It is significant that several reports were received from some quite small practices while many larger practices filed no reports at all. This suggests that there is an element of under reporting which may be happening for a variety of reasons."

Anecdotal evidence supports the proposition that adverse reactions are underreported in the veterinary and oncology literature. A review of Internet discussion boards in 2007 turned up the following posts [39] by dog owners who believed their pets had suffered adverse reactions from microchip implants .

Cancer: *"My mothers dog 'Buddy' actually lost his life to a 'large' malignant sarcoma that was located on his back by the chip. It was removed once, but aggressively grew back and quickly took his life. I strongly believe this Chip is what took his life."*

Transponder failure: *"My cocker spaniel, Cooper...has two microchips in him. The first one quit working, so he was implanted with a second one."*

Swelling: *"My dogs [sic] problem with microchip [is] swelling area around microchip, even to about 4 cm big, it goes away after a course of AB [antibiotics]."*

Lump: *"Jack was microchipped at his first vet visit when we got him - oh so many years ago...I'm wondering - now that he is a senior citizen, I feel a small lump where the microchip was implanted - I am assuming it's only scar tissue and my vet has backed that up."*

Bleeding: *"[W]hen Myrl was microchipped, the vet was very rough and he bled a LOT. She kind of stabbed him with the injector and he yelped and his white fur turned red. It was horrible."*

None of these incidents appears to have been formally reported to any agency or decision-making body, and a review of the literature indicates that none has been written up by the academic veterinary community. Similarly, although reports of chip-related neurological damage and infection in horses have begun to appear on the Internet, few, if any, reports of adverse microchip reactions in horses have been reported in the literature.

Even when pet owners contact veterinarians and researchers to report their adverse experiences, they often find it difficult to get a response. Jeanne, the owner of Leon, the bulldog whose chip-related tumor is described by Vascellari et al. [11], reports her frustration at how difficult it was to find a veterinary professional or researcher that would pay attention to what had happened. Her quest to tell Leon's story became almost a full- time endeavor as she searched the globe for a veterinary oncologist willing to look at the evidence and investigate the tumor [40, 41].

It is clear that veterinary oncologists and others need to open a better dialog with members of the public around these important issues and that a better mechanism for reporting adverse reactions is needed.

7. What Do These Findings Mean for People?

As discussed previously, it is known that humans are susceptible to foreign-body carcinogenesis, though they appear to be less susceptible than rodents. As a foreign body, the microchip implant could potentially give rise to tumors within human beings.

The long-term effects of implanted microchips in human beings are presently unknown. Most human microchips have been implanted since the VeriChip implant received FDA approval for use as a medical device in October 2004. With less than years of data available on a very small number of people, it is difficult

to draw definitive conclusions about the safety of the device. If humans follow a similar pattern of microchip-induced cancer development as that observed in mice and rats, we would not expect to see implant-induced malignancies until half a lifetime's exposure, or approximately 30-40 years.

This researcher is aware of no formal follow-up procedure to evaluate the health effects or the long-term safety of implanted microchips in human patients. The lack of a formal evaluation procedure and a means of publicly reporting adverse reactions that is well-understood by patients means that any such reactions would likely go unreported to the public or to the FDA.

7.1. The Toxic Cocktail Effect

There is a further consideration in this day of increasing carcinogen exposure. Research indicates that exposure to multiple carcinogens, even within safe levels, can result in cancer development at rates that exceed what would be expected from the individual carcinogens alone. This has been called the "toxic cocktail" effect [42].

The microchip-induced tumors observed in the Elcock et al. study [6] described in this paper may have been an example of this effect. In that study, only rats exposed to a test chemical developed malignant tumors around the microchips. However, even rats exposed to a very low dose of the chemical compound developed the malignancies. It may be that the microchip, when combined with even small doses of a chemical compound, worked together to bring about a cancerous response.

It is estimated that inhabitants of the modern world are exposed to 75,000 artificial chemicals daily [42]. Given the high rate of exposure to chemical compounds, it would seem prudent to avoid unnecessary or elective exposure to additional potential cancer-causing agents such as implanted foreign bodies, both in ourselves and our pets.

8. Recommendations

The following recommendations are proposed for physicians, policy-makers, veterinarians, pet owners, and veterinary researchers in light of research findings on microchip implants.

8.1. For Human Patients and Their Doctors

There are many unanswered questions about the safety of microchip implants in human beings, but what we know from animal studies is disquieting. In light of the serious adverse reactions seen in animals, it is the opinion of this researcher that the practice of chipping human beings should be immediately discontinued until the tumorigenesis process is more fully understood.

All patients, members of the public, and medical volunteers who have been implanted with microchips to date (an estimated 300 people in the United States and 2,000 people worldwide) should be immediately informed in writing of the causal link between microchips and cancer in rodents and dogs. Implanted individuals should be offered a procedure for microchip removal at the expense of the facility that provided the implant, should they choose to have the device removed. Following the advice of Jennings et al., the tissue surrounding all removed implants should be histologically examined.

Should a patient chose to retain an implanted microchip, his or her physician should routinely examine the tissue surrounding the implant for swelling, inflammation, evidence of chip migration, or pain. Any unusual sensations, lumps, or other abnormalities should be analyzed for cancerous or pre-cancerous changes. All adverse reactions, whether related to cancer or other problems, should be immediately reported to the FDA for disclosure in the public record.

8.2. For Policy-Makers

Given the clear, causal link between microchip implants and malignant tumors in laboratory rodents and dogs, it is strongly recommended that policy makers reverse all policies that mandate the microchipping of animals under their jurisdiction or control. These include ordinances passed by state and local authorities, policies implemented at animal shelters, and formal positions adopted by animal welfare, affinity, and interest groups across the United States and around the globe.

It is the opinion of this researcher that mandatory microchipping ordinances should be repealed and replaced with a voluntary system of microchipping at the discretion of pet owners. Any pet owner who chooses to have a microchip implanted in his or her animal should be fully informed of the potential risks of the procedure. No one should be forced by law or otherwise coerced into implanting an animal against his or her conscience or medical judgment.

8.3. For Veterinarians

Veterinary offices are among the most likely places for implant procedures to be performed. Since veterinarians are often the primary point of contact for pet owners on the topic of microchipping, veterinarians should familiarize themselves with the research findings and carefully consider the potential for adverse reactions before recommending implants for their patients.

Pet owners should be clearly advised of the research linking the microchip to cancer in rodents and dogs when

seeking advice about the chipping procedure or requesting the procedure for their pets.

In the case of animals that have already been implanted, Vascellari et al. suggest that veterinary surgeons should routinely palpate the tissue surrounding microchip implants as part of routine medical care. Any lumps or inflammation should be investigated for cancerous or pre-cancerous changes. To avoid the complicating risk of injection-related sarcoma, veterinarians should avoid administering vaccines or other injections at or near the site of an implanted microchip.

Finally, veterinarians should advise pet owners to routinely examine the site of the implanted microchip themselves and immediately report any abnormalities.

8.4. For Pet Owners

There have been no large-scale, statistically valid, clinically controlled, experimental studies involving microchip implants in dogs and cats, so we know very little about their long-term safety. However, the fact that we have not seen an epidemic of cancers in pets would suggest that only a small number will be impacted. As the chip-removal procedure may be both costly and invasive, pet owners may wish to leave the implanted microchips intact within their animals unless a problem surfaces.

Owners of pets that have been implanted should regularly check the area around the chip for any abnormal lumps or swelling. If something unusual is found, it should be immediately reported to a veterinarian, and tests should be done to rule out cancer. The pet owner may be the key to detecting a problem in the early stages and saving the life of a pet. In the two cases where dogs developed tumors around and attached to implants, it was the owners' astute eye and probing fingers that found the cancers, not the veterinarian. The only indication that there was a problem was the lump; all other laboratory tests came back within normal ranges.

If a pet is not currently microchipped, it may be best to keep it that way. It is the opinion of this researcher that all further implantation of pets should be halted until the existing population of chipped dogs is carefully assessed for adverse reactions, including cancer. There are other ways to ensure a pet is returned to its owner in the event it goes missing. A well-made collar and a clear, legible tag with the owner's contact information are effective tools that have worked for generations of pet owners.

8.5. For Veterinary Oncology Researchers

There is fertile ground for additional research in this area, and systematic study would add greatly to our understanding of the process of tumorigenesis as related to microchip implants. Other than preliminary research involving very small number of animals (e.g., Ball et al.; Rao and Edmondson), there have been no studies to date that have systematically examined the development of microchip- induced sarcomas as a research goal in itself. Almost all of the cancers reported herein arose incidentally, in the course of other research.

One important direction for future research would be to explore the role played by electromagnetic energy transmitted by the transponder. This could help determine whether the tumors stem from a foreign-body reaction to the external surface of the microchip alone (i.e. glass capsule and polypropylene sheath) or whether some characteristic of the device in its capacity as a radio-frequency transponder could be responsible for the tumors. A study could be designed to investigate the role of radio-frequency energy by implanting some animals with intact transponder devices and others with empty capsules. In each of these groups, animals could be exposed to different levels of energy from the reader, as well.

8.6. Proposal to Create a National Registry

The research community should take advantage of the fact that there are already millions of chipped dogs in the U.S. Rather than conducting further, potentially painful and invasive studies on dogs and other animals, we can study animals that are already chipped to learn more about how living creatures respond to these devices.

Doing so would require the creation of a central registry for reporting adverse reactions to microchips, including cancer. A registry could be created in one of the following ways:

- Dogs undergoing treatment for cancer could be voluntarily reported to an independent registry set up for this purpose. Because microchip-induced cancer may metastasize and lead to cancer in other parts of the body, it is important to rule out the microchip as the source of cancer in dogs. Veterinarians would report the chip status of all dogs with cancer under their care, and a statistical analysis could be made to determine whether chipped dogs have a higher overall incidence of cancer than their non-chipped counterparts.
- On a voluntary basis, veterinarians could remove the microchip and surrounding tissue from deceased pets and send them to a laboratory for histological analysis.

Done on a large scale, these measures would provide important data that could be used to assess the safety of microchip implants in dogs. Establishing national registries for adverse reactions and evaluating tissue samples would provide a more systematic way of assessing the risk than the current state of relying on case-by-case and anecdotal reports alone.

9. Conclusion

The body of research reviewed in this report indicates a clear causal link between microchip implants and cancer in mice and rats. It also appears that microchips can cause cancer in dogs–and that they have done so in at least one case, and quite likely in two. These findings raise a red flag about the continued use of microchips in both animals and human beings.

As the Associated Press reported, this concern is shared by some of the nation's most respected cancer researchers.

"There's no way in the world, having read this information, that I would have one of those chips implanted in my skin, or in one of my family members," said Dr. Robert Benezra, head of the Cancer Biology Genetics Program at the Memorial Sloan-Kettering Cancer Center in New York. He added, "Given the preliminary animal data, it looks to me that there's definitely cause for concern."

Dr. George Demetri, director of the Center for Sarcoma and Bone Oncology at the Dana-Farber Cancer Institute in Boston, agreed. Even though the tumor incidences were "reasonably small," in his view, the research underscored "certainly real risks" in RFID implants, adding that the tumors can be "incredibly aggressive and can kill people in three to six months."

Dr. Chand Khanna, a veterinary oncologist at the National Cancer Institute, said that the evidence "does suggest some reason to be concerned about tumor formations." All of the cancer specialists agreed the animal study findings should be disclosed to anyone considering a chip implant.

On the basis of these findings, physicians, patients, veterinarians, and pet owners may wish to carefully consider whether the benefits of implants are worth the potential health risks such implants appear to pose. It is the opinion of this researcher that further microchipping of pets or human beings should be immediately discontinued.

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